REMARKS

Applicants thank the Examiner for examining the present application and preparing the office action dated August 18, 2006.

After amendment, claims 1, 2, and 4-30 will be pending in this application, with claims 17 and 24-30 withdrawn from consideration.

Former claims 1, 2, 10-16, and 18-23 were rejected under 35 USC 112, ¶1; and former claims 1-16 and 18-23 were rejected under 35 USC 103(a) over Kauvar *et al.*, US Patent No. 5955432 in view of Kauvar *et al.*, US Patent No. 5556942, as evidenced by the USP Dictionary of USAN and International Drug Names, 2005. These rejections, to the extent they are considered applicable to the amended claims, are respectfully traversed.

**The Amendment**

Entry of the amendment is respectfully requested. No new matter is added by the amendment, because the amended claims find full support in the application as filed. Claim 1 has been amended by writing into it the definition of the GST-activated anticancer compound from (now-cancelled) claim 3. Claim 3 has been cancelled; claim 4 has been amended to depend from claim 1; and claim 10 has been amended to no longer depend from claim 3. Claim 21 has been amended in the same manner as claim 1, thereby incorporating the definition of the GST-activated anticancer compound from (now-cancelled) claim 3, and replacing anticancer "agent" with anticancer "compound" for consistency. Claim 23 has also been amended to replace anticancer "agent" with anticancer "compound".

Withdrawn claims 25, 27, and 29 have also been amended to replace anticancer "agent" with anticancer "compound", though the full definition of claim 3 has not been written into those claims.

**The 35 USC 112, ¶1 rejection**

Former claims 1, 2, 10-16, and 18-23 were rejected under 35 USC 112, ¶1 for failure to comply with the written description requirement, with the Office Action stating that "The claims encompass a genus of compounds defined solely by its principal biological activity, i.e.

GST-activated, which is simply a wish to know the identity of any material with that biological property. However, the written description in this case only sets forth a GST-activated anticancer compound having the formula shown in claim 3."

Applicants respectfully disagree.

This assertion that, for example, claim 1 encompasses "a genus of compounds defined *solely* by its principal biological activity" (emphasis added) is incorrect because it ignores the totality of Applicants' definition of a GST-activated anticancer compound. Paragraph **[0034]** of the application states that "A 'GST-activated anticancer compound' is a compound comprising glutathione or a glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes." This is far more than defining the genus "solely by its principal biological activity" – the genus is of compounds that are defined *chemically* by comprising glutathione or a glutathione analog chemically linked to a cytotoxic moiety, with the linkage having the additional *biological* limitation that the cytotoxic moiety shall be released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes.

However, in the interest of expediting the prosecution of this application, Applicants have limited the now-claimed GST-activated anticancer compounds to those of former claim 3, which the Office Action agrees comply with the written description requirement ("the GST-activated anticancer compound of the formula shown in claim 3 … meets the written description provision" of 35 USC 112, ¶1 – Office Action at page 4, third full paragraph.) Applicants reserve the right to file continuing application(s) to claim the canceled subject matter.

Withdrawal of the rejection under 35 USC 112, ¶1 is respectfully requested in view of the amendment.

**The 35 USC 103(a) rejection**

Former claims 1-16 and 18-23 were rejected under 35 USC 103(a) as being unpatentable over Kauvar *et al.*, US Patent No. 5955432 (referred to in the Office Action as "Kauvar '432") in

view of Kauvar *et al.*, US Patent No. 5556942 ("Kauvar '942"), as evidenced by the USP Dictionary of USAN and International Drug Names, 2005. This rejection is respectfully traversed as applied to amended claims 1, 2, 4-16, and 18-22.

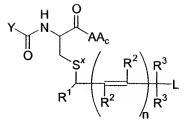
Claim 1 recites "A method of combination cancer therapy in a mammal comprising administering a therapeutically effective amount of a GST-activated anticancer compound and a therapeutically effective amount of another anticancer therapy" (emphasis added). Claims 2, 4-16, and 18-22 are directly or indirectly dependent on claim 1.

The Office Action states that:

> "Kauvar '432 teaches a method of protecting a subject from the destructive effects of a chemotherapeutic agent, including irradiation, comprising administering to a subject an effective dose of a glutathione analog (column 2, lines 48-55). ***
>
> Kauvar et al. [*sic*, presumably Kauvar '432] do not explicitly teach that the glutathione analog is a GST-activated anticancer compound."

Applicants do not disagree that Kauvar '432 teaches glutathione analogs. However, not only does Kauvar '432 "not explicitly teach that the glutathione analog is a GST-activated anticancer compound", the glutathione analogs of Kauvar '432 *are not* GST-activated anticancer compounds.

Applicants' definition of a GST-activated anticancer compound is found in paragraph **[0034]**, which states that "A 'GST-activated anticancer compound' is a compound comprising glutathione or a glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes." Further, following the amendment made in this response, the *claimed* GST-activated anticancer compound is further limited to being "a compound of the formula



or an amide, ester, or salt thereof, where:

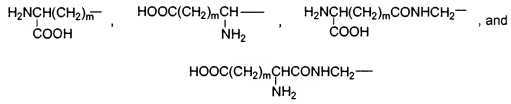
L is a cytotoxic electron withdrawing leaving group;

$S^x$ is –S(=O)-, -S(=O)$_2$-, -S(=NH)-, -S(=O)(=NH)-, -$S^+$($C_1$-$C_6$ alkyl)-, -Se(=O)-, -Se(=O)$_2$-, -Se(=NH)-, or –Se(=O)(=NH)-, or is -O-C(=O)-, or -HN-C(=O)-;

each of $R^1$, $R^2$ and $R^3$ is independently H or a non-interfering substituent;

n is 0, 1 or 2;

Y is selected from the group consisting of



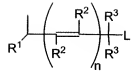
where m is 1 or 2; and

$AA_c$ is an amino acid linked through a peptide bond to the remainder of the compound."

The glutathione analogs of Kauvar '432 are not the GST-activated anticancer compounds of the present claims because, although they contain glutathione or a glutathione analog, they do not contain that glutathione or a glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes: there is neither cytotoxic moiety [X in formula (1) of Kauvar '432 is a $C_{1-20}$ hydrocarbon radical] nor GST-cleavable linkage [Z in formula (1) is $CH_2$, O, or S]. They are also not compounds of the formula of amended claim 1 for the same reasons:

(a) $S^x$ in the formula does not include $CH_2$, O, or S; and

(b) the remainder of the sidechain



does not include $C_{1-20}$ hydrocarbyl.

Applicants do not dispute that Kauvar '942 discloses the class of GST-activated anticancer agents claimed in amended claims 1, 2, 4-16, and 18-22, including TER286, and their salts (although canfosfamide hydrochloride is not specifically disclosed); and also do not dispute that the USP Dictionary of USAN and International Drug Names, 2005, entry for canfosfamide hydrochloride discloses canfosfamide hydrochloride and demonstrates that TER286 and canfosfamide are the same. Applicants therefore do not dispute that canfosfamide hydrochloride is a GST-activated anticancer agent within the definition of paragraph **[0034]**.

The Office Action reasons that "it would have been *prima facie* obvious … to substitute the glutathione derivatives taught by Kauvar '432 with a GST-activated compound as taught by Kauvar '942 because each of the agents have been individually taught in the prior art to be effective at mitigating the bone-marrow destructive effects of chemotherapeutic agents" and that the compounds of Kauvar '942 are also useful for selective treatment of target tissues which contain compatible GST isoenzymes, so that there would be reasonable expectation of success that "by administering a GST-activated anticancer compound in combination with a chemotherapeutic agent, one would achieve a method of treating cancer" as well as a method of mitigating the bone-marrow destructive effects of chemotherapeutic agents such as cisplatin.

With regard to a rejection under 35 USC 103(a), MPEP 2143 states:
"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of

success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

First, there is no suggestion or motivation to combine the teachings of Kauvar '432 and Kauvar '942 because the glutathione analogs of Kauvar '432 are GST isoenzyme inhibitors, not GST-activated anticancer compounds. Applicants do not dispute that Kauvar '432 describes the glutathione analogs as useful in potentiating the effects of cytotoxic agents, but the glutathione analogs themselves are not anticancer agents, they are GST isoenzyme inhibitors. Thus Kauvar '432 does not provide suggestion or motivation to replace the glutathione analog GST isoenzyme inhibitors with an anticancer agent, still less the particular GST-activated anticancer agents of Kauvar '942. Nor do Kauvar '942 provide any suggestion or motivation to use their GST-activated anticancer agents in combination cancer therapy – they propose that the compounds may be used by themselves. Finally, while a person of ordinary skill in the art may be aware of combination cancer therapy, that knowledge is so general and the number of anticancer agents so great that it cannot be said that such general knowledge provides motivation for the combination of any particular pair of references such as Kauvar '432 and Kauvar '942 here.

The statement in the Office Action that "one would have been motivated to do so because each of the agents have been individually taught in the prior art to be effective at mitigating the bone-marrow destructive effects of chemotherapeutic agents" is not to the contrary. Nothing in Kauvar '942 suggests the use of its GST-activated anticancer compounds in combination cancer therapy or that a GST isoenzyme inhibitor would be useful in combination cancer therapy (since Kauvar '942 do not disclose GST isoenzyme inhibitors), and equally nothing in Kauvar '432 suggests that a GST-activated anticancer compound would be useful in combination cancer therapy because Kauvar '432 talk about GST isoenzyme inhibitors and not about GST-activated anticancer compounds, and give no reason to substitute a GST-activated anticancer compound for the glutathione analog – since such a substitution would lose the GST isoenzyme inhibitory effect of the glutathione analog and therefore the asserted combination cancer therapy benefit which is based on that GST isoenzyme inhibitory activity. It is as if one were to say that because, for example, amlodipine, atenolol, captopril, hydrochlorothiazide, and minoxidil are all

antihypertensives (they, along with about another 200 compounds, are so listed in the *Merck Index*, 14th Edition – see pages THER-10 and THER-11 for the list), a person of ordinary skill in the art would consider it appropriate to substitute one for another. No physician would do so – commonality of effect and substitutability cannot be equated. Or, in the oncology setting, it is as if one were to say that because cisplatin, carboplatin, and oxaliplatin are all platinum-containing anticancer compounds, a person of ordinary skill in the art would consider it appropriate to substitute one for another. No oncologist would do so – similarity of structure and substitutability cannot be equated. For example, cisplatin and carboplatin are both used in lung cancer, whereas oxaliplatin is not – it is inactive in that disease; however, oxaliplatin is used in colon cancer where cisplatin and carboplatin are inactive.

The Office Action also reasons that "it would have been *prima facie* obvious … to combine the chemotherapeutic agents taught by Kauvar '432 with a GST-activated anticancer compound as taught by Kauvar '942 because each of the agents have been individually taught in the prior art to be effective at treating cancer", citing *In re Kerkhoven*, 205 USPQ 169 (CCPA 1980) for the proposition that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art for the same purpose to form a third composition that is to be used for the same purpose.

Applicants respectfully disagree. While *Kerkhoven* suggests that combining compositions known to be equivalent *under the facts of that case* for the same purpose was *prima facie* obvious, cases such as *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) teach that there is no presumption of obviousness in combination ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been *prima facie* obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive.... Appellant argues... hindsight reconstruction or at best,... 'obvious to try'.... We agree with appellant.").

It is indisputable that cancer chemotherapeutic agents are not equivalent one for another *in general*, although certain small groups of cancer chemotherapeutic agents are regarded as sufficiently therapeutically similar that one may be substituted for another. It is also indisputable that cancer chemotherapeutic agents are not combinable just for the reason that they are cancer chemotherapeutic agents – they are not for a number of reasons, not least that the toxicities of two agents, each of which is tolerable alone, may combine to make the combination regimen unacceptably toxic. Applicants submit that there is no suggestion or motivation in the prior art to combine the chemotherapeutic agents taught by Kauvar '432 with a GST-activated anticancer compound as taught by Kauvar '942 "because each of the agents have been individually taught in the prior art to be effective at treating cancer" – the fact that the chemotherapeutic agents *taught in Kauvar '432 as being potentiatable by the glutathione analogs of Kauvar '432* are chemotherapeutic agents and the GST-activated anticancer compound of Kauvar '942 is also a chemotherapeutic agent *does not* provide motivation for the combination in view of the well-known difficulties of combination cancer chemotherapy.

Second, there is no reasonable expectation of success in the proposed combination. This is true because, as explained above, there is no motivation for the combination. With no motivation, *a fortiori* there can be no expectation of success. And consider the cisplatin/carboplatin/oxaliplatin example mentioned above as negating any general expectation of success in simply substituting one chemotherapeutic agent for another.

Since there is no teaching or suggestion to make the claimed combination nor any reasonable expectation of success in the prior art cited in the Office Action, no *prima facie* case of obviousness has been made out.

Applicants have unexpectedly discovered that a GST-activated anticancer agent as claimed in amended claim 1 and its dependent claims is combinable with another anticancer therapy with beneficial effect and relative lack of increase in toxicity, and that this is unobvious in view of the cited art.

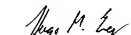
By not arguing the other aspects of the rejection (e.g. dosing), Applicants do not intend to be considered to agree with the Office Action's expression of those aspects – they are not being argued here because the issue of non-disclosure of a GST-activated anticancer compound by Kauvar '432, and hence the non-combinability of Kauvar '432 and Kauvar '942 (the non-substitutability of the GST-activated anticancer compounds of Kauvar '942 for the GST isoenzyme inhibitors of Kauvar '432), is dispositive of the propriety of the rejection.

Withdrawal of the rejection of amended claims 1, 2, 4-16, and 18-22 is respectfully requested.

Applicants respectfully submit that all pending rejections have been addressed and that the present application is now in condition for allowance. Favorable reconsideration and allowance of the pending claims is respectfully requested. If the Examiner believes a telephone conversation would help advance prosecution of the present application, the Examiner is cordially invited to contact the undersigned at the number below.

Respectfully submitted,

Date 20 February 2007

By 

FOLEY & LARDNER LLP
1530 Page Mill Road
Palo Alto, California 94304-1125
Telephone: (650) 251-1126
Facsimile: (650) 856-3710

Hugo M. Eng, Ph.D.
Registration No. 50,840